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AMERSHAM BIOSCIENCES
PATENT DEPARTMENT
800 CENTENNIAL AVENUE
PISCATAWAY, NJ 08855

EXAMINER	
WILDER, CYNTHIA B	

ART UNIT	PAPER NUMBER
1637	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/022,014	BRUSH ET AL.	
	Examiner	Art Unit	
	Cynthia B. Wilder, Ph.D.	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 August 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-39* is/are pending in the application.

4a) Of the above claim(s) *15-39* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

FINAL ACTION

1. Applicant's amendment filed August 15, 2004 is acknowledged and has been entered. Claim 1 has been amended. Claims 15-39 are withdrawn from consideration as being drawn to a non-elected invention. Claims 1-39 are pending in the instant invention. Claims 1-14 are discussed in this Office action. All of the arguments have been thoroughly reviewed and considered but are not found persuasive for the reasons discussed below. Any rejection not reiterated in this action has been withdrawn as being obviated by the amendment of the claims.

This action is made FINAL.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Previous Rejections

3. The prior art rejections under 35 USC 102(b) are maintained and discussed below. The prior art rejections under 35 USC 103(a) are maintained and discussed below.

Claim Rejections - 35 USC § 102

4. Once again, claims 1, 10-13 are rejected under 35 U.S.C. 102(b) as being anticipated by Monforte et al (US 5,830,655, November 3, 1998). Regarding claim 1, teach an assay comprising contacting a target nucleic acid with a oligonucleotide immobilized on an array, under conditions that allow hybridization, said target nucleic acid having at least one phosphorothioate moiety (col. 6, lines 4-23 and col. 10, lines 1-63).

Regarding claim 10 and 12, Monforte et al teach the method of claim 1, wherein at least one nucleotide is a ribonucleotide or is a deoxynucleotide (col. 6, lines 18 and col. 10, line 1-2).

Regarding claims 11 and 13, Monforte et al teach the method of claims 10 or 12, wherein the target nucleic acid comprises from up to four different thiodeoxyribonucleotides. The reference also teaches the use thio-modified nucleosides (page col. 21, line 62 to col. 22, line 2). The reference further inherently implies the use of thio-ribonucleotides in the teaching of the target comprising RNA (page 10, lines 1-2, 10-14, 23-26 and 51-55). Therefore, Monforte et al meets the limitations of claims 1, 10-13 of the instant invention.

5. Once again, claims 1-7, 10 are rejected under 35 U.S.C. 102(b) as being anticipated by Wong et al (US 6,120,997, September 19, 2000). Regarding claim 1-3, Wong et al teach a method comprising contacting a target nucleic acid with probe immobilized on a microarray under conditions that allow hybridization, said target nucleic acid having at least one phosphorothioate moiety. Wong et al teach further comprising labeling said target nucleic acid by conjugating a reporter molecule to said phosphorothioate moiety (col. 8, lines 52-67, col. 28-32; col. 19, 42-48, and col. 20, lines 2-5).

Regarding claim 5-7, Wong et al teach the method of claim 2, wherein said reporter molecule has an electrophilic moiety comprising iodoacetamide (col. 19, lines 46-48).

Regarding claim 10, Wong et al teach wherein at least one nucleotide is a ribonucleotide (col. 19, lines 42-48). Therefore, Wong et al meets the limitations of claims 1-7 and 10 of the instant invention.

Applicant's Traversal

6. Applicant traverses the rejections under 35 USC 102 on the following grounds: Applicant summarizes the Examiner's rejections and states that the methodology of the instant invention is quite different from that disclosed in the Montfonte '655 patent, inasmuch as the

instant methodology relates to an expression assay whereas the '655 patent is related to methodology to provide "more useful sizing and sequence information per fragment than extension products containing the entire primer. Applicant states to emphasize the difference, Applicant has amended the claim 1, upon which claims 2-13 ultimately depend to be in Jepson format; this claim, Applicant respectfully submits, that the claimed methodology is directed to an expression assay as an unambiguous and integral part of the claim. In Regards to the Wong et al document, Applicant asserts that, like the Montforte et al patent, the Wong et al patent neither discloses nor even suggests an expression assay as claimed in the captioned application. Applicant request the rejections be withdrawn.

Examiner's Response

7. All of the amendments and arguments have been thoroughly reviewed and considered but are not found persuasive for the reasons that follow: In response to Applicant's arguments that the patent of Montforte and Wong et al do not teach or even suggests an expression assay as claimed in the instant invention, it is noted that the claims as currently amendment only defines "an expression assay" as binding of a target to a microarray of immobilized probes. There is no nexus between the limitation "expression assay" and the steps of "binding a target to a microarray of immobilized probes..." nor is their any nexus between the use of the term "expression assay" and *known* steps associated with expression. While it is noted that Applicant has amended the claims to be in a Jepson format, it is noted that the claims as written to do not describe or disclose any steps of "expression", but rather only describes steps of "binding". Therefore, there is *no nexus* between the use of the term "expression assay" and the claimed methods step recited therein. Contrary to Applicant's arguments, Applicant has defined

"an expression assay" as only comprising binding of a target molecule to a microarray of immobilized probes". Both Montforte and Wong et al meet the limitations of the claims of the instant invention because they teach the steps as required by the instant invention (see prior Office action). Applicant's arguments are not sufficient to overcome the prior art rejections of Montfonte et al and Wong et al. Accordingly, the rejections are maintained.

Claim Rejections - 35 USC § 103

8. Once again, claims 1-8, 12 and 14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chee et al (WO 98/56954, December 1998) in view of Fidanza et al (Journal of American Chemical Society, Vol. 111, pages 9117-9119) and Housby et al (TIBTECH, vol. 18, pages 439-440, November 2000). Regarding claims 1-8, 12 and 14, Chee et al teach an expression assay, comprising contacting a target nucleic acid with a probe immobilized on an array under conditions that allow hybridization with said target and said probe, said target comprising a label, wherein said label is a florescent label or biotin. Chee et al further teach wherein at least one nucleotide is a ribonucleotide or deoxyribonucleotide and wherein said target is selected from the group consisting of RNA, DNA, cDNA or cRNA (page 4, line 10 to page 5, line 51; page 12, line 13-15, 23-25 and 31; page 15, lines 13-21).

Chee et al differs from the instant invention in that the reference does not teach wherein said target comprises a nucleic acid having at least one phosphorothioate moiety.

Fidanza et al teach the covalent attachment of reporter groups at specific sites within oligonucleotide sequences using phosphorothioate conjugation with iodacetamide. Fidanza et al teaches that phosphorothioate diesters at specific sites within DNA fragments can be employed

to direct the covalent attachment of reporter groups such as fluorophores spin labels, or drug derivatives to the sugar phosphate backbone. Fidanza et al further teaches that attaching reporter groups (covalently) wherein desired on the DNA backbone allow detailed studies in structure and function and should simplify studies involving protein binding (see entire reference, pages 9117-9119).

Housby et al provides a general teaching of microarrays and their use in methodologies, which relies on oligonucleotides conjugated with a phosphorothioate moiety. Housby et al teach that an obvious use for microarray technology is in the field of pharmacogenomics. Housby teach that Klaus Giese reported the identification of novel drug target using the proprietary GENEBLOC antisense technology and DNA arrays. Housby et al teach that the inhibitors are oligonucleotides that contain a mixture of 2' methyl ribose and deoxynucleotides with phosphorothioate modification of the phosphate backbone. Housby et al teach that Giese claimed that these molecules are specific for the intended target genes, have low toxicity, are resistant to nuclease and have a high target-binding affinity. Housby et al teach that it was suggested that these molecules might be useful in monitoring gene expression changes during disease progression, and also in studying the effects of gene inhibition on signaling pathways and differential gene expression (page 439, col. 2 and 3, entire section entitle "Pharmacogenomics").

One of ordinary skill in the art at the time of the claimed invention would have been motivated to have modified the detection method of Chee et al to encompass Fidanza et al's conjugation in order to increase facility of attaching reporter groups for the benefit of studying structure and function of target nucleic acids as suggested by Fidanza et al.

One of ordinary skill in the art would have been further motivated to modify the detection method of Chee et al to encompass Fidanza et al's conjugation with a reasonable expectation of success based on the teaching of Housby et al that these molecules are specific for the intended target genes, have a high target-binding affinity and might be useful in monitoring gene expression during disease progression, gene inhibition of pathways and differential gene expression (see citation above).

Applicant's Traversal

9. Applicant's traverses the rejections on the following ground: Applicant summarizes the examiner's rejection and asserts that the Examiner has not properly combined the teachings of the references to form a rejection under 35 USC 103(a). Specifically, Applicant states that the reference of Chee et al discloses and claims methodology for detecting genetic polymorphisms and monitoring of allelic expression using a probe array and acknowledged that the reference does teach that determination of DNA and RNA hybridization profiles, as well as hybridization intensities, can be utilized to characterize specific genotype and/or expression profiles. Applicant contend however that the reference does not disclose, nor even suggest, including phosphorothiate conjugation to allow for the attachment of reporter molecules at various stages within the DNA RNA molecules. Applicant further contends that Fidanza et al reference discloses a method of covalently attaching reporter groups at specific sites within DNA sequences, which "would simplify detailed study of the structure and dynamics of unusual DNA forms as well as ligand-DNA or protein-DNA complexes"; continuing this attachment methodology bond to an appropriately labeled reporter group. Applicant further contends that figure 1 discloses a number of labels which can be attached to DNA molecule, including a

PROXYL spin label, a derivative of dihydropyrroloindole subunits, sulfonamide-linked dansyl fluorophores, and the reference notes that these labeled DNA molecules are quite stable and that structural studies of DNA molecules can be determined. Applicant assert that Fidanza et al reference provides no disclosure, nor even any suggestion, that such methodology would be adaptable, or even useful, in a probe assay of the type disclosed in the '954 PCT publication. Further, Applicants point out that there is no disclosure, nor even any suggestion that the methodology would be useful with RNA expression studies. Applicants states that while the Examiner states that the motivation for combining theses references would be to increase facility of attaching reporter groups, the Fidanza et al and Chee et al references do not alone or even in combination with each other, remotely suggests that attachment chemistry would be useful or even desirable in expression assay methodology. Applicant further asserts that at best the Examiner has shown that it would be "obvious to try" to utilize the attachment chemistry disclosed in the Fidanza et al article in the methodology of Chee et al PCT publication. Applicant contends that the Examiner is reading something into the cited references that is neither disclosed nor suggested. Applicant states that more specifically, while Applicants concede that the Chee et al, application does disclose methodology for the measurement of the expression level of polymorphic forms of a gene using a probe assay, Applicants emphasize that it does not disclose, nor even suggest, the inclusion of a phosphorothioate moiety in the target nucleic acid. Applicant states that such phosphorothioate moiety will facilitate the attachment of reporter molecules. With regards to the Examiner's statement that Housby provides a reasonable expectation of success, that these molecule are specific for the intended target genes, have a high target-binding affinity and might be useful in monitoring gene expression during

disease progression, gene inhibition of pathways and differential gene expression, Applicant asserts that Housby reference neither discloses nor even suggest the same composition as the Chee et al and Fidanza et al reference. Applicant states that while the compounds disclosed have some similarity to those of Chee et al and Fidanza et al, Applicant submit that there is no basis upon which to believe that the composition would behave identically. Applicant further assert that one skilled in the art would not be led to believe the teaching of Chee et al and Fidanza et al could be extended as the Examiner has suggested. Applicant states that it is only with the teaching of the instant invention as presented in the captioned application, that such is seen.

Examiner's response

10. All of Applicant's arguments have been thoroughly reviewed and considered but are not found persuasive for the reasons that follow: In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). It is firstly noted, that the claims as written do not provide any limiting definition as to what correlates to an expression assay. *The claims as written only require that the "expression assay" comprise "binding between a target and probe on a microarray in the presence of a phosphorothioate moiety.* In this case, the primary reference of Chee et al was applied for its teaching of an assay comprising a target molecule binding to a

microarray comprising immobilized probes. Chee et al discloses that the method can be used to monitor variations in gene expression associated with a disease or disorder and further teach the incorporation of a reporter molecule (label) onto the target. As indicated in the prior Office action, Chee does not teach the use of phosphorothioate moiety attached to DNA or RNA. The secondary reference of Fidanza was applied to provide a teaching of phosphorothioate moieties being attached to DNA. Fidanza et al further teach the importance of attaching phosphorothioate moieties at specific sites within DNA fragments for the benefit of studying DNA structure and function (see prior Office action for citation). The tertiary reference of Housby was applied to further support that DNA molecules comprising phosphorothioate moieties can be utilized in microarray technologies, which is indicated by Chee et al. Housby provides motivation for wanting to attach phosphorothioate moieties at specific sites within DNA fragments and further supports that it would be obvious for one of ordinary skill in the art to use these molecules in gene expression assays such as that taught by Chee et al. To reiterate the previous Office action, Housby teaches that molecules containing the phosphorothioate moiety are specific for an intended target gene, have a high target-binding affinity and may be useful for monitoring gene expression during disease progression, gene inhibition of pathways and differential gene expression. Thus contrary to Applicant's arguments, the combination of the references do not provide an "obviousness to try" scenario but rather provides motivation for wanting to use DNA molecules comprising phosphorothioate moieties in a general binding assay for structure/function analysis or in a gene expression assay to monitor disease progression. In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a

sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). As stated earlier, the Examiner's asserts that the combination of references cited therein provides an obviousness teaching of the instant invention because the combination of the Chee et al in view of Fidanza et al in and Housby provides a reasonable expectation of success for carrying out the binding methodology on a microarray in the presence of a phosphorothioate moiety. As indicated earlier, the use of the term "expression assay" in the claim as written does not limit the claim as Applicant argues because no clear nexus between the claimed method steps and any type of known expression is set forth. Thus one cannot be clear what constitutes an "expression assay" in the context of the claims as written. One can only rely on the method steps as indicated in the claims. In this case, Chee provides the binding assay. Fidanza et al provides steps of attaching phosphorothioate moiety to DNA and Housby provides motivation for using such molecules in microarray technologies, which like Chee, can be used in gene expression studies to monitor the progression of a disease or condition. In regards to Applicant's arguments that the Examiner is reading something into the cited references that is neither disclosed nor suggested, it is again noted that the reference of Chee was not cited for its teachings of a phosphorothioate moiety but rather for its teaching of a target molecule binding to a microarray comprising immobilized probes. With respect to Applicant's arguments that a phosphorothioate moiety would facilitate the attachment of reporter molecules, it is noted that Chee et al teach the use of reporter molecules (labels) attached to the target molecule for

identification and measurement of polymorphic alleles. Hence, this argument further supports that the use of a phosphorothioate moiety to the target molecule, which facilitates attachment of reporter molecules, would be beneficial in the method of Chee et al to identify and measure polymorphic forms of a gene. Finally, in regards to Applicant's arguments that while the compounds of Housby et al have some similarity to Chee et al and Fidanza et al, there is no basis to believe that the composition would behave identically, it is noted that there is no basis given by Applicant to believe that the composition would not behave identically, specifically since the combination of references teaches microarray technologies and phosphorothioate moiety being attached to DNA as well as their use in gene expression analysis. Applicant's arguments are not sufficient to overcome the prior art rejections under 35 USC 103(a). Accordingly, the rejections are maintained.

Claim Rejections - 35 USC § 103

11. Once again, claim 9 is rejected under 35 U.S.C. 103(a) as being unpatentable over Chee et al in view of Fidanza et al and Housby et al as applied to claims 1-8, 12 and 14 above, and further in view Karger et al (US 5,348,633,September 20, 1994). Regarding claim 9, Chee et al in view of Fidanza et al and Housby et al teach an expression assay and an array with probes which binds to labeled target nucleic acids, wherein said labeling comprises conjugating a reporter molecule (e.g., fluorophore) to a phosphorothioate moiety attached to the target.

The references differ from the instant invention in that they do not teach wherein said reporter molecule is TMR-maleimide, TMR-iodoacetamide or ALEXAFLUOR-maleimide.

Karger et al discloses et al use of reporter molecules in methods of labeling target molecules. Karger et al teach that a useful reporter molecule should possess strong absorbance

and high fluorescence yield in order to produce a measurable signal during analysis. Karger et al further teach that the fluorophore should not photobleach significantly during the method of detection and should be pH insensitive. Karger et al teach that the preferred reporter molecules as fluorescent labeling groups are tetramethylrhodamine iodoacetamide (col. 4, line 66 to col. 5, line 15).

One of ordinary skill in the art would have been motivated to have modified the detection method of Chee et al in view of Fidanza et al and Housby to encompass the use of the reporter molecule, tetramethylrhodamine iodoacetamide as the labeling group based on the characteristics and advantages taught by Karger et al that a molecule, such tetramethylrhodamine iodoacetamide possess strong absorbance, high fluorescence yield and produce a measurable signal during analysis.

Applicant's Traversal

12. Applicant traverses the rejection on the following ground: Applicant summarizes the Examiner's rejection and reiterates the arguments presented above as to the inapplicability of the Chee et al, Fidanza et al and Housby et al reference and respectfully asserts that the addition of Karger et al does nothing to remedy theses deficiencies. Applicant asserts that the Examiner's rejections cannot be sustained and should be withdrawn.

Examiner's Response

13. All of the arguments have been thoroughly reviewed and considered but are not found persuasive for the reasons previously discussed above at #10. The examiner asserts that the addition of Karger et al teach the limitations not found in Chee et al in view of Fidanza et al and Housby et al. Motivation can be found in the reference of Karger et al for the combinations of

references recited therein (see previous Office Action). Applicant's arguments are not sufficient to overcome the rejection under 35 USC 103(a). Accordingly, the rejection is maintained.

New ground(s) of Rejection

THE NEW GROUNDS OF REJECTIONS WERE NECESSITATED BY APPLICANT'S AMENDMENT OF THE CLAIMS:

Claim Rejections - 35 USC § 112

14. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

15. Claims 1-14 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

(a) Claims 1-14 are indefinite and confusing in the Jepson format because the claims set forth steps involved in "a binding assay", but recite wherein the assay is "an expression assay". Thus, there is no correlation or nexus between "expression" and *known* steps associated with expression. Clarification is required as to Applicant's intent.

Conclusion

16. No claims are allowed. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Cynthia B. Wilder, Ph.D. whose telephone number is (571) 272-0791. The examiner works a flexible schedule and can be reached by phone and voice mail. Alternatively, a request for a return telephone call may be emailed to cynthia.wilder@uspto.gov. Since email communications may not be secure, it is suggested that information in such request be limited to name, phone number, and the best time to return the call.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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KENNETH R. HORLICK, PH.D
PRIMARY EXAMINER

10/27/05